REMARKS

Claims 37-39 are pending in the present application. Claims 1-36 have been cancelled without prejudice or disclaimer to the subject matter recited therein. Claims 37-39 have been newly added.

New claim 37 is directed to "A method of prophylaxis or treatment of cystic fibrosis comprising: administering a tricyclic or tetracyclic antidepressant or substances derived from a tricyclic or tetracyclic antidepressant." Claims 38-39 depend from claim 37. Support for new claims 37-37 can be found, for example, in cancelled claims 20, 22 and 31, as well as at page 3, paragraph 29, of the specification as originally filed.

No new matter has been added within the meaning of 35 USC § 132.

In view of the following, further and favorable consideration is respectfully requested.

Rejection Under 35 U.S.C. § 112

Claims 20, 22, 24, 33 and 35-36 are rejected under 35 USC § 112, second paragraph, as being indefinite. The Examiner asserts that the phrase "in particular" renders the claims indefinite.

Applicant notes that claims 20, 22, 24, 33 and 35-36 have been cancelled without prejudice or disclaimer. Applicant respectfully submits that the rejection of claims 20, 22, 24, 33 and 35-36 has been rendered moot by the cancelation of the claims. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Claim Objection

Claim 23 has been objected to because of a typographical error.

Applicant notes that claim 23 has been cancelled without prejudice or disclaimer. Applicant respectfully submits that the objection to claim 23 has been rendered moot by the cancelation of the claim. Accordingly, the Examiner is respectfully requested to withdraw this objection.

Rejection Under 35 USC § 101

Claims 19-32 have been rejected under 35 USC § 101. Specifically the Examiner asserts that the claimed recitation of a use does not set forth any steps involved in the process.

Applicant notes that claims 19-32 have been cancelled without prejudice or disclaimer. Applicant respectfully submits that the rejection of claims 19-32 has been rendered moot by the cancelation of the claims. Accordingly, the Examiner is respectfully

requested to withdraw this rejection.

Rejection Under 35 USC § 112

Claims 19-36 have been rejected under 35 USC § 112, first paragraph. Specifically, the Examiner asserts that specification is not enabling for methods for prophylaxis of infectious diseases or diseases influenced by infection or making the pharmaceutical compositions as claimed.

Applicant notes that claims 19-36 have been cancelled without prejudice or disclaimer. Applicant respectfully submits that the rejection of claims 19-36 has been rendered moot by the cancelation of the claims. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejection Under 35 USC § 112

Claims 19-32 have been rejected under 35 USC § 112, second paragraph, as being indefinite. Specifically, the Examiner asserts that it is unclear what method/process the claims intend to encompass.

Applicant notes that claims 19-32 have been cancelled without prejudice or disclaimer. Applicant respectfully submits that the rejection of claims 19-32 has been rendered moot by the cancelation of the claims. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejection Under 35 USC § 102

Claims 19, 24, 26-30 and 34-36 have been rejected under 35 USC § 102(b) as being anticipated by Grasseme et al. (Grassmé, H., et al., "CD95 Signaling Via Ceramide-Rich Membrane Rafts," The Journal Of Biological Chemistry, Vol. 276, No. 23, pp. 20589-20596, (2001)).

Applicant notes that claims 19, 24, 26-30 and 34-36 have been cancelled without prejudice or disclaimer. Applicant respectfully submits that the rejection of claims 19, 24, 26-30 and 34-36 has been rendered moot by the cancelation of the claims. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejection Under 35 USC § 102

Claims 19-22, 27, 29 and 33 are rejected under 35 USC § 102(b) as being anticipated by Hauck et al. (Hauck, C.R., et al., "Acid Sphingomyelinase Is Involved In CEACAM Receptor-Mediated Phagocytosis Of *Neisseria gonorrhoeae*," FEBS Letters, Vol. 478, Pgs. 260-266, (2000)).

Applicant notes that claims 19-22, 27, 29 and 33 have been cancelled without prejudice or disclaimer. Applicant respectfully submits that the rejection of claims 19-22, 27, 29 and 33 has been rendered moot by the cancelation of the claims. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Rejection Under 35 USC § 103

Claims 19-36 have been rejected under 35 USC § 103(a) as being unpatentable over Grassme et al. as applied to claims 19, 24 and 26-30 above and Hauck et al. as applied to claims 19-21, 27 and 29-30 above, and in further view of Claus et al. (Claus, S.R., et al.,

"Modulation Of The Ceramide Level, A Novel Therapeutic Concept?," Current Drug Targets, Vol. 1, No. 2, Pgs. 185-205, (2000)) and Haimovitz-Friedman et al. (Haimovitz-Friedman, A. et al., "Lipopolysaccharide induces disseminated endothelial apptosis requiring ceramide generation (1997) J. Exp. Med., 186 (11): 1831-1841). Specifically, the Examiner asserts that an artisan seeking to identify new drug targets against infectious disease pathogens would have combined the teachings of Grassme et al. and Hauck et al., thus allegedly identifying the acidic sphingomyelinase. Additionally, the Examiner asserts that a person of ordinary skill in the art would have found it obvious utilize the teachings of drug treatments effective as inhibitors of the ASM/ceramide pathway taught by Grassme et al., Claus et al. and Haimovitz-Friedman et al. to generate the presently claimed methods and compositions.

Applicant notes that claims 19-36 have been cancelled without prejudice or disclaimer. Applicant respectfully submits that the rejection of claims 19-36 has been rendered moot by the cancelation of the claims. Accordingly, the Examiner is respectfully requested to withdraw this rejection.

Newly Added Claims 37-39

As discussed above, new claim 37 directed to "A method of prophylaxis or treatment of cystic fibrosis comprising: administering a tricyclic or tetracyclic antidepressant or substances derived from a tricyclic or tetracyclic antidepressant." Claims 38-39 depend from claim 37. Support for new claims 37-37 can be found, for example, in cancelled claims 20, 22 and 31, as well as at page 3, paragraph 29, of the specification as originally filed.

Applicant respectfully submits that new claims 37-39 are: directed to patentable subject matter within the meaning of 35 USC § 101; clear and definite within the meaning of 35 USC § 112, second paragraph; fully enabled by the specification within the meaning of 35

USC § 112, first paragraph; and, neither anticipated nor rendered obvious by any of Grassme et al., Hauck et al., Claus et al. and Haimovitz-Friedman et al.

In support of the patentability of the presently claimed subject matter, Applicant submits herewith a copy each of Figures 1-3 as well as a copy of Teichgraber et al., "Ceramide accumulation mediates inflammation, cell death and infection susceptibility in cystic fibrosis mice."

Figures 1-3 are graphic representations of data obtained by the present inventor. Briefly, as known to those skilled in the art cystic fibrosis (CF) is a hereditary disease that affects the lungs and digestive function in an infected subject. CF causes a progressive disabling of the subject. CF is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR). The product of CFTR is a chloride ion channel that plays an important role in functions including, for example, creating sweat, digestive juices and mucus.

Applicant submits that based on experiments conducted on Cftr-knockout-mice, Applicant has observed an increased concentration of ceramide in the lungs. As known to those skilled in the art, Cftr is the mouse equivalent to the human CFTR. Applicant notes that Cftr-knockout-mice are a reliable animal model for cystic fibrosis. A defective Cftr contributes to increased pH levels in intracellular vesicles of lung cells. In this regard, the enzyme ceramidase, which degrades ceramide, is more greatly inhibited by the increased pH levels than the enzyme acid sphingomyelinase, which produces ceramide. Consequently, ceramide accumulates in the intracellular vesicle of lung cells. The ceramide accumulation causes cellular death, and therefore causes a release of cellular components. Specifically, DNA is released in the bronchial tubes. Infectious pathogens can easily bind to the released cellular components, leading to increased microbial colonization. In particular, pseudomonades increase in the lung.

Figure 1 is a graphical representation of comparison of the activity of the enzyme acid sphingomyelinase in the lung extracts of various wild type mice and Cftr-deficient mice. The y-axis shows the level of activity of the enzyme. The numbers on the x-axis refer to the type of mice being compared. In this regard, numbers 1-8 represent the following:

1. Untreated wild type mice;
2. Untreated Cftr-deficient mice;
3. Wild type mice, wherein the enzyme activity has been measured 60 minutes after inhalation of 1ml of amitriptyline solution (4 mg per liter H_2O);
4. Cftr-deficient mice, wherein the enzyme activity has been measured 60 minutes after inhalation of 1ml of amitriptyline solution (4 mg per liter H_2O);
5. Wild type mice, wherein the enzyme activity has been measured 12 hours after inhalation of 1ml of amitriptyline solution (4 mg per liter H_2O);
6. Cftr-deficient mice, wherein the enzyme activity has been measured 12 hours after inhalation of 1ml of amitriptyline solution (4 mg per liter H_2O);
7. Wild type mice, wherein the enzyme activity has been measured 12 hours after intraperitoneal injection of 250 μg of amitriptyline; and
8. Cftr-deficient mice, wherein the enzyme activity has been measured 12 hours after intraperitoneal injection of 250 μg of amitriptyline.

Applicant respectfully submits that the results represented in figure 1 show that a significant inhibition of acid sphingomyelinase is achieved by treatment with amitriptyline. In this regard, Applicant notes that inhibition of the enzyme ranges between 55 and 66 percent of total cellular activity of acid sphingomyelinase in the lung extracts of Cftr-deficient mice. Therefore, Applicant submits that the activity of acid sphingomyelinase is significantly reduced by the administration of amitriptyline.

Figure 2 is a graphical representation of a comparison of the ceramide concentration in the lung extracts of various wild type mice and Cftr-deficient mice. The y-axis shows the ceramide concentration. The numbers on the x-axis refer to the type of mice being compared. In this regard, numbers 1-8 represent the following:

1. Untreated wild type mice;
2. Untreated Cftr-deficient mice;

3. Wild type mice, wherein the enzyme activity has been measured 12 hours after inhalation of 1ml of amitriptyline solution (4 mg per liter H_2O);
4. Cftr-deficient mice, wherein the enzyme activity has been measured 12 hours after inhalation of 1ml of amitriptyline solution (4 mg per liter H_2O);
5. Wild type mice, wherein the enzyme activity has been measured 12 hours after intraperitoneal injection of 250 μg of amitriptyline; and
6. Cftr-deficient mice, wherein the enzyme activity has been measured 12 hours after intraperitoneal injection of 250 μg of amitriptyline.

Applicant respectfully submits that the results represented in figure 2 show that the administration of amitriptyline leads to a significant normalization of the pulmonary ceramide levels in the lung extracts of Cftr-deficient mice.

Figure 3 is a graphical representation of a colony forming units (CFU) of the pseudomonas aeruginosa strain 762 in the lung extracts of wild type mice and Cftr-deficient mice. The treated mice of groups 3-6 were administered the respective dose of amitriptyline as a preventative treatment. Following administration of amitriptyline the mice were intranasally infected strain 762. The y-axis shows the CFU measured in the lung extracts of the various test groups. The numbers on the x-axis refer to the groups of mice being compared. In this regard, numbers 1-8 represent the following:

1. Untreated wild type mice;
2. Untreated Cftr-deficient mice;
3. Wild type mice treated by inhalation of 1 ml of amitriptyline solution (4 mg per liter H_2O);
4. Cftr-deficient mice treated by inhalation of 1ml of amitriptyline solution (4 mg per liter H_2O);
5. Wild type mice treated by intraperitoneal injection of 250 μg of amitriptyline; and
6. Cftr-deficient mice treated by intraperitoneal injection of 250 μg of amitriptyline.

Applicant respectfully submits figure 3 shows that the administration of amitriptyline leads to a normalization in the susceptibility of the Cftr-deficient mice to infection caused by pseudomonas aeruginosa.

Additionally, Applicant submits that Teichgraber et al., i.e., "Ceramide accumulation mediates inflammation, cell death and infection susceptibility in cystic fibrosis mice," further supports the assertion that amitriptyline and related substances are suitable therapeutic agents for the treatment of cystic fibrosis. According to Teichgraber et al., pharmacological treatment of CF-mice with amitriptyline normalizes pulmonary ceramide and prevents pathological findings, including susceptibility to infection. *See,* for example, pages 48-46 and figures 1a, 2e, 2f, 3a, 3b and 3c, as well as generally pages 27-41 and the Abstract. Applicants respectfully submit that the enclosed Teichgraber et al. has been accepted for publication in Nature Medicine. Therefore, Applicants submit that Teichgraber et al. supports the present subject matter in that it provides evidence that CF may be successfully treated with amitriptyline.

Regarding the art cited in the present Official Action, Applicants reiterate the position that none of Grassme et al., Hauck et al., Claus et al. and Haimovitz-Friedman et al. either anticipate or render the presently claimed subject matter obvious.

Briefly, the test for anticipation is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California,* 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP § 2131. The identical invention must be shown in as complete detail as is contained in the claim. R*ichardson v. Suzuki Motor Co.,* 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond,* 15 USPQ2d 1566 (Fed. Cir. 1990).

Additionally, to establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court very recently held in *KSR International Co. v. Teleflex Inc. et al.*, Slip Opinion No. 04–1350, 550 U. S. ____ (April 30, 2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look

to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

It is submitted that none of Grassme et al., Hauck et al., Claus et al. and Haimovitz-Friedman et al. either anticipate or render the presently claimed subject matter obvious because, whether taken alone or in combination, none of the cited references teach or suggest each and every element of the present claims. Specifically, none of Grassme et al., Hauck et al., Claus et al. and Haimovitz-Friedman et al. teach or suggest a method of prophylaxis or treatment of cystic fibrosis comprising: administering a tricyclic or tetracyclic antidepressant or substances derived from a tricyclic or tetracyclic antidepressant.

In contrast to the present subject matter, Grassme et al. is describes that the acid sphingomyelinase mediated release of ceramide and/or metabolites of ceramide regulate clustering of CD40. Additionally, Grassme et al. indicate that the aforementioned regulation of clustering appears to be a prerequisite for cellular activation via CD40. *See* Grassme et al. at the abstract. However, Grassme et al. do not teach or suggest a method of prophylaxis or treatment of cystic fibrosis comprising: administering a tricyclic or tetracyclic antidepressant

or substances derived from a tricyclic or tetracyclic antidepressant, as presently claimed.

Hauck et al. do not remedy the deficiencies of Grassme et al. Hauck et al. is directed showing that CEACAM receptor-mediated phagocytosis of Opa_{52}-expressing N. gonorrhea into human cells results in a rapid activation of the acid sphingomyelinase. *See* Hauck et al. at the abstract. However, Hauck et al. do not teach or suggest a method of prophylaxis or treatment of cystic fibrosis comprising: administering a tricyclic or tetracyclic antidepressant or substances derived from a tricyclic or tetracyclic antidepressant, as presently claimed. Therefore, whether taken alone or in combination, none of Grassme et al. or Hauck et al. teach or suggest every element of the present claims.

Claus et al. do not remedy the deficiencies of Grassme et al. and Hauck et al. Claus et al. is directed to the role of SMases in signaling pathways. Further, Clause et al. describe potential contributions of SMases in the development and maintenance of various path biological states. Additionally, Claus et al analyze the perspective of a potentially isotoype-specific inhibition of SMases as a novel therapeutic concept. *See* Claus et al. at the abstract. However, Claus et al. do not teach or suggest a method of prophylaxis or treatment of cystic fibrosis comprising: administering a tricyclic or tetracyclic antidepressant or substances derived from a tricyclic or tetracyclic antidepressant, as presently claimed. Therefore, whether taken alone or in combination, none of Grassme et al., Hauck et al. and Claus et al. teach or suggest every element of the present claims.

Haimovitz-Friedman et al. do not remedy the deficiencies of Grassme et al. Hauck et al. and Claus et al. Haimovitz-Friedman et al. is directed to demonstrating that LPS induces a disseminated form of endothelial apoptosis, mediated sequentially by TNF and ceramide generation. Additionally Haimovitz-Friedman et al. suggest that the aforementioned cascade is mandatory for evolution of the endotoxic system. *See* Haimovitz-Friedman et al. at the abstract. However, Haimovitz-Friedman et al. do not teach or suggest a method of prophylaxis or treatment of cystic fibrosis comprising: administering a tricyclic or tetracyclic

antidepressant or substances derived from a tricyclic or tetracyclic antidepressant, as presently claimed. Therefore, whether taken alone or in combination, none of Grassme et al., Hauck et al., Claus et al. and Haimovitz-Friedman teach or suggest every element of the present claims.

In view of the foregoing, it is submitted that the presently claimed subject matter is: are: directed to patentable subject matter within the meaning of 35 USC § 101; clear and definite within the meaning of 35 USC § 112, second paragraph; fully enabled by the specification within the meaning of 35 USC § 112, first paragraph; and neither anticipated nor rendered obvious by any of Grassme et al., Hauck et al., Claus et al. and Haimovitz-Friedman et al. Accordingly, Applicant submits that the present application is in condition for immediate allowance.

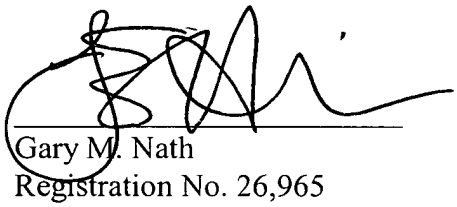
CONCLUSION

In view of the foregoing, Applicant submits that the application is in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicant petitions for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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